(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 267 702**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 87309254.8

(22) Date of filing: 20.10.87

(51) Int. Cl.4: A61K 9/14 , A61K 9/20 , A61K 9/68

Claims for the following Contracting States: GR + ES.

(30) Priority: 21.10.86 US 921658

(43) Date of publication of application: 18.05.88 Bulletin 88/20

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

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(54) Spray dried acetaminophen.

(57) A therapeutic taste-neutral powder form of acetaminophen is obtained by spray-drying a dispersion of acetaminophen and ethyl cellulose in water having a plasticizer dissolved or suspended therein. The powder can be formulated into fast dissolving dosage forms, chewable tablets and the like.

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SPRAY DRIED ACETAMINOPHEN

This invention relates to a novel therapeutic form of spray dried acetaminophen having a neutral taste which can b formulated into, for example, chewable tablets and fast dissolving dosage forms as described in United States Letters Patent Nos. 4,305,502 and 4,371,516 and UK Patent Specification No. 1,548,022. More specifically this invention relates to a spray dried powder formed by spray drying a dispersion of acetaminophen and ethylcellulose in water having a plasticiser dissolved or suspended therein. The spray dried powder may be taste-neutral. By "taste-neutral" it is meant that the powder has essentially no taste and is not sweet nor bitter.

Acetaminophen (otherwise known as paracetamol), a widely used analgesic and antipyretic, is not palatable enough to be used in chew-type tablets for those people who do not swallow whole solid-type dosage forms.

The use of flavor agents e.g. chocolate, banana, orange, lemon, licorice, root beer, and raspberry, in particular, have been proposed for bitter tasting drugs. These agents are not dependable masking ingredients. Mint flavors can be useful in ameliorating a chalky taste parameter. Bitter properties, however, are very difficult to mask to any great extent, particularly, when they do not mimic the expected natural taste of the flavor agent.

Other properties including mouthfeel also need to be addressed in consideration of the oral acceptance of chewable or chew-type tablets.

The fast dissolving dosage forms described in United States Letters Patent Nos.4,305,502 and 4,317,516 and UK patent specification 1,548,022 are manufactured to disintegrate in water within ten seconds e.g. within five seconds or less and hence dissolve rapidly in the saliva of the mouth. Such dosage forms for oral administration can comprise a network of a pharmaceutically acceptable water-soluble or water-dispersible carrier material (e.g. gelatin) carrying a unit dosage of pharmaceutical substance, the carrier material being inert towards the pharmaceutical substance, the network having been obtained by subliming solvent from a composition in the solid state, the composition comprising the pharmaceutical substance and a solution of the carrier material in a solvent such that the dosage form is capable of being disintegrated by water within ten seconds. Heretofore the use of such dosage forms was restricted to pharmaceuticals which had a neutral taste or a slightly disagreeable taste which could be masked by a flavouring agent. Pharmaceuticals with a bitter taste such as acetaminophen, however, could not heretofore be used in such dosage forms.

According to this invention, a novel therapeutic taste-neutral powder form of spray-dried acetaminophen is provided which can be formulated into chewable tablets and the like. The powder is formed by spray drying a dispersion of acetaminophen and ethyl cellulose in water having a plasticiser dissolved or suspended therein.

The invention particularly provides a therapeutic powder form of spray-dried acetaminophen which consists essentially of, based upon the weight of the powder, about 63% to 77% by weight acetaminophen, about 15% to 30% by weight ethylcellulose and about 2% to 7% by weight of a plasticizer, the powder having been spray dried from a dispersion of the acetaminophen and ethyl cellulose in water having a plasticizer dissolved or suspended therein.

According to another aspect of this invention, a pharmaceutical dosage form for oral administration as a solid is provided, which dosage form can be disintegrated by water at 37° within ten seconds, and comprises as the pharmaceutical agent incorporated therein the powder form of spray dried acetaminophen of this invention.

The acetaminophen useful in this invention may be the pharmaceutical grade. The ethyl cellulose useful in this invention may also be National Formulary or pharmaceutical grade. Suitable grades include the AQUACOAT brand marketed by FMC Corporation of Newark, New Jersey and the SURELEASE brand marketed by Colorcon Incorporated, West Point, Pennsylvania.

The plasticisers useful in this invention include dibutyl sebacate, glycerin, propylene glycol, triacetin and low molecular weight polyethylene glycols such as CARBOWAX 600, marketed by Union Carbide Corp. of Danbury, Connecticut. A preferred plasticizer is UNIFLEX brand of dibutyl sebacate marketed by Union Camp Corp. of Jacksonville, Florida.

The weight percent of acetaminophen in the taste neutral powder can be from about 63% to 77% by weight and the weight percent of the ethylcellulose can range from 15% to 30% by weight. At 15% by weight of ethylcellulose, there is no bitter taste and the powder is taste neutral. The weight percent of plasticizer in the taste neutral powder can be from about 2% to 7% by weight.

Spray dryers can be of the usual laboratory or commercial type. Suitable spray dryers are manufac-

tured by Buchi Laboratoriums-Technik AG, by the Anhydro Company of Attleboro, Massachusetts and by Niro Atomizer Inc., of Columbia, Maryland.

The following examples illustrate the invention. In these examples, the ethyl cellulose was obtained from FMC Corporation, Newark, New Jersey as AQUACOAT. It was a 30% solids dispersion in water of the standard type having a viscosity designation of 10 and an ethoxy content of 48.0% to 49.5%.

EXAMPLE 1

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient in suspension
Acetaminophen, USP	70	210
AQUACOAT brand of Ethyl Cellulose, NF	25	249
Uniflex brand of Dibutyl Sebacate	5	15
Deionized Water-	--	1200
Total:	100%	≈ 1674 grams

Approximately 280 grams of finely divided acetaminophen was passed through a 35 mesh (Tyler) screen and 210 grams of the screened acetaminophen was dispersed in 1200 grams of deionized water using a homogenizer mixer. The dispersion was then mixed with a Lightnin mixer while adding 249 grams of AQUACOAT brand of ethyl cellulose as a 30% solids dispersion in water followed by the 15 grams of dibutyl sebacate. The mixing was continued for 75 minutes. The dispersion was then transferred to the feed hopper of the Buchi Portable Spray Dryer.

The spray dryer employed in this example was a Buchi 190 Mini Spray Dryer. The operating conditions for the Buchi Mini Spray Drier are customarily an inlet temperature of 220°C and an outlet temperature of 130°C.

The spray drier was operated such that an air inlet temperature of approximately 210°C and an air outlet temperature of approximately 140°C was maintained throughout the run.

The product was a white, fine powder. The product upon tasting produced no bitterness characteristic of acetaminophen and was practically tasteless.

Dissolution data were obtained on capsules containing the spray dried product of this example using the USP procedure. The spray dried product in the amount of 114 milligrams containing 80 milligrams of acetaminophen was placed in each capsule and six capsules were used in each test. The data show that at a pH of 5-7 seventy-five per cent of the acetaminophen was dissolved from one-half of the capsules in about 20 to 30 minutes and dissolution of seventy-five per cent of the acetaminophen was not achieved in 30 minutes in the other one-half of the capsules.

EXAMPLE 2

In this xample, th feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient in suspension
Acetaminophen, USP	70	140
AQUACOAT brand of Ethyl Cellulose, NF	25	166
Uniflex brand of Dibutyl Sebacate	5	10
Deionized Water-	--	1600
Total:	100%	≈1916 grams

Approxmiately 160 grams of finely divided acetaminophen were passed through a 20 mesh (Tyler) screen and 140 grams of the screened acetaminophen were dispersed in 1600 grams of deionized water contained in a mixing vessel equipped with a Lightnin mixer. The dispersion was then mixed for 10 minutes. 166 grams of AQUACOAT brand of ethyl cellulose as a 30% solids dispersion in water were then added and mixed for 10 minutes and then the 10 grams of dibutyl sebacate were added. The dispersion was then transferred to the feed hopper of the spray dryer.

The spray dryer employed in this example was a Niro Portable Spray dryer, Model No. 21231-000L. The operating conditions include a variable air inlet temperature, a variable outlet temperature, a variable air pressure of compressed air driving the atomizer wheel, and a variable feed rate.

The spray drier was operated such that an air inlet temperature of approximately 150° to 155°C was maintained throughout the run. An air outlet temperature was recorded at 100° to 105°C[3]

The product was a fine, white powder which had a neutral taste.

EXAMPLE 3

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient per 2kg suspension
Acetaminophen, USP	71.8	125
AQUACOAT brand of Ethyl Cellulose, NF	25.7	148.6
Uniflex brand of Dibutyl Sebacate	2.5	4.4
Deionized Water-	----	1722
Total:	100%	≈ 2000grams

To the 148.6 grams of AQUACOAT brand of ethyl cellulose as a 30% solids dispersion in water contained in a mixing vessel equipped with a paddle mixer and a Lightnin mixer were added the 4.4 grams of dibutyl sebacate and the dispersion was mixed for 10 minutes. The 125 grams of acetaminophen

prescreened through 20 mesh (Tyler) followed by 200 grams of deionized water were added and mixed for one hour. The remaining water, 1522 grams, was then added and th disp rsion was transferred to the fe d hopper of the Niro Portable Spray Drier used in Example 2.

Th spray drier was operated such that an air inlet temperature of approximately 200-210°C was maintained throughout the run. An air outlet temperature was recorded at 85°-95°C.

The product was a fine, white powder which had a neutral taste.

EXAMPLE 4

This example describes the preparation of fast dissolving dosage forms using the spray dried taste-neutral acetaminophen of Example 2 and other ingredients as follows:

Ingredients	Weight % suspension	Grams Ingredients per 500 grams suspension
Gelatin, BY 19/50	4.0	20.00
Mannitol, granular	3.0	15.00
Deionized water	67.5	337.5
NUTRASWEET, NF	0.6	3.00
Anise/Juicy Fruit #669	0.75	3.75
Red FD&C #40 (1% Solution)	0.25	1.25
Sodium lauryl sulfate	1.0	5.00
Sweetness Flavor # 284	0.1	0.5
Powder, Example 2	22.8	114
Total:	100	500

The procedure for preparing a batch of the above suspension takes place in two stages, i.e. the preparation of the gelatin base and the addition of the pharmaceutical agent.

The gelatin base is prepared by adding the gelatin to the deionized water at 30°C and mixing until the gelatin is dissolved. The solution is then cooled to 25°C and the mannitol, the sodium lauryl sulfate, the sweetener, and the flavors are separately added and dissolved.

The freeze drier employed in this example was a Virtis 25 SRC Model Freeze Drier. The fast dissolving dosage forms were prepared by dosing 500 milligrams of the suspension of acetaminophen into each well in a thermoformed blister tray containing 10 wells per tray. The filled trays were placed in a larger tray containing a dry ice-methanol mixture. When the suspension in the wells were frozen, the samples were placed on the freeze dryer trays at a shelf temperature of -45°C.

When the samples had reached a temperature of -45°C, as determined by a probe in a well, the condenser was turned on and the freezer turned off. The condenser temperature was brought to between -40° and -45°C and the vacuum was turned on to between 50 and 60 millitorrs. The heater was then turned on and the shelf temperature was adjusted to 50°-55°C. The heat-dry cycle lasted for 4 hours. The vacuum, the condenser and the heater were turned off and the samples removed. The wafers from each batch were removed from the wells in the trays. They were white in color and each weighed about 165 milligrams of which about 80 milligrams was acetaminophen. The wafers from each batch when placed on the tongue exhibited a fruit flavor with a very slight bitter after taste. When placed in water at 37°C the wafers disintegrated in less than ten seconds.

EXAMPLE 5

This example describes the preparation of a chewable tablet using the spray dried taste neutral acetaminophen of Example 2 and other ingredients as follows:

Ingredients	Weight
Powder of Example 2,70%	500mg
Aluminum Stearate	2mg
Sorbitol	q.s. to 700mg
Total	700mg

The powder of Example 2 contained 70% by weight or 350 mg of acetaminophen. The ingredients are mixed in a suitable mixer and formed into tablets. The tablets when chewed in the mouth have a neutral taste and good mouthfeel. The taste could be improved by incorporation into the tablet of suitable flavoring agents such as a mint flavoring agent.

Claims

1. A therapeutic powder form of spray-dried acetaminophen which consists essentially of, based upon the weight of the powder, about 63% to 77% by weight acetaminophen, about 15% to 30% by weight ethylcellulose and about 2% to 7% by weight of a plasticizer, the powder having been spray dried from a dispersion of the acetaminophen and ethyl cellulose in water having a plasticizer dissolved or suspended therein.

2. A powder as claimed in claim 1 in which the plasticizer is dibutyl sebacate, glycerin, propylene glycol, triacetin or a polyethylene glycol.

3. A process for preparing a therapeutic powder form of spray dried acetaminophen consisting essentially of, based upon the weight of the powder, about 63% to 77% by weight acetaminophen, about 15% to 30% weight ethylcellulose and about 2% to 7% by weight of a plasticizer which comprises spray drying a dispersion of the acetaminophen and ethyl cellulose in water having the plasticizer dissolved or suspended therein.

4. A process as claimed in claim 3 whereas the plasticizer is dibutyl sebacate, glycerin, propylene glycol, triacetin or a polyethylene glycol.

5. A pharmaceutical dosage form for oral administration as a solid, which dosage form can be disintegrated by water within ten seconds characterised in that it contains a therapeutic powder as claimed in claim 1 or 2.

6. A solid pharmaceutical dosage form for oral administration which comprises a network of a pharmaceutically acceptable water-soluble or water-dispensible carrier material carrying a unit dosage of pharmaceutical substance, the carrier material being inert towards the pharmaceutical substance, the network having been obtained by subliming solvent from a composition in the solid state, the composition comprising the pharmaceutical substance and a solution of the carrier material in a solvent, such that the solid dosage form is capable of being disintegrated by water within ten seconds, characterised in that the pharmaceutical substance is a therapeutic powder as claimed in claim 1 or 2.

7. A chewable tablet containing a powder as claimed in claim 1 or 2.

Claims for the following Contracting States: ES, GR

1. A process for preparing a therapeutic powder form of spray-dried acetaminophen which consists essentially of, based upon the weight of the powder, about 63% to 77% by weight acetaminophen, about 15% to 30% by weight ethyl cellulos and about 2% to 7% by weight of a plasticizer which comprises spray drying a dispersion of the acetaminophen and ethyl cellulose in water having a plasticizer dissolved or suspended therein.

2. A process as claimed in claim 1 in which the plasticizer is dibutyl sebacate, glycerin, propylene glycol, triacetin or a polyethylene glycol.

3. A process as claimed in claim 1 or 2 in which the resulting therapeutic powder is incorporated as the pharmaceutical substance in a pharmaceutical dosage form for oral administration as a solid, which dosage form can be disintegrated by water within ten seconds.

4. A process as claimed in claim 1 or 2 in which the resulting therapeutic powder is incorporated as the pharmaceutical substance in a chewable tablet for oral administration.